REMARKS

The Official Action mailed May 19, 1993, has been reviewed. Reconsideration of the rejections is respectfully requested.

The Applicants thank the Examiner for the telephonic interview with Applicants' representative, Thomas A. Turano, held on July 7, 1993. The interview confirmed that claims 25 and 26 were withdrawn when the Applicants responded to the restriction requirement in the Official Action of October 21, 1992. Therefore, the Applicants are not responding to the rejections directed to claims 25 and 26.

Figs. 1-5 are objected to under 37 CFR 1.84.

Claims 1-45 remain in prosecution. Claims 1-45 have been made subject to a species restriction requirement. The species embodied in claims 1 and 7 have been elected for continued prosecution. Claims 1-12, 25, 26, and 29-36 were subject to a further restriction requirement under 35 USC §121 made by the Examiner in the Official Action of October 21, 1992. The Applicants elected to prosecute claims 1-12 and 29-36 drawn to a radiolabelled composition and a kit for its use.

Claims 1-12 and 29-36 stand rejected.

The Examiner has objected to Figs. 1-5 under 37 CFR 1.84. The Applicants have included herein proposed corrections to the figures with changes indicated in red for the Examiner's approval. The Applicants submit that the further objections and requirements as to form made by the Examiner are not necessary to further consideration of the claims, and therefore respectfully request

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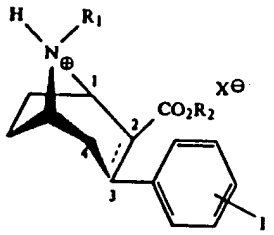
that these objections be held in abeyance until allowable subject matter is indicated.

The Applicants have amended the specification to include the material in the figure legends of Figs. 2, 5A, and 5B as originally filed. Therefore, the Applicants submit that no new matter has been added.

The Examiner has rejected claims 1-12 Under 35 USC §102(e) as being anticipated by Carroll et al. The Applicants respectfully traverse this rejection.

Anticipation requires that every element of the claim, arranged as in the claim, is identically shown by a single prior art reference. Carroll et al. disclose a compound of the formula:



where the broken line represents an optional chemical bond and the substituents at 2 and 3 may be at any position; the iodo substituent may be at o, m, or p, or multisubstituted; R_1 is CH_3, $CH_2CH{=}CH_2$, $(CH_2)_nC_6H_5$ where n=1-4; R_2 is CH_3, C_2H_5, $CH_3(CH_2)_3$, $(CH_3)CH$, C_6H_5, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$; X is a pharmacologically acceptable anion; and the iodo substituent is radioactive.

The Applicants have amended independent claims 1 and 7 to recite an iodinated neuroprobe for mapping monoamine reuptake

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sites, the iodinated neuroprobe being of the formulas shown above, wherein

R = a monofluoroalkyl group including ^{n}F where n=18 or 19;

R′ = a C_nH_{2n+1} group where n=0-6;

X = an isotope of F, an isotope of Cl, an isotope of Br, an isotope of I; CH_3, or $Sn(R"_1R"_2R"_3)$;

$R"_1$ = a C_nH_{2n+1} group where n=1-6, or an aryl group;

$R"_2$ = a C_nH_{2n+1} group where n=1-6, or an aryl group;

$R"_3$ = a C_nH_{2n+1} group where n=1-6, or an aryl group; and

Y = H.

As recited above, Carroll et al. do not teach a monofluoroalkyl group including ^{n}F where n=18 or 19 at the R position. Further, claims 1 and 7 of the present invention do not recite a $CH_2CH=CH_2$ group or a $(CH_2)_nC_6H_5$ group where n=1-4 at the R position as recited in Carroll et al. Moreover, the Applicants have herein cancelled claims 2, 3, 8, and 9 directed towards p-iodophenylmethyl and p-iodophenylethyl groups incorporating radioactive isotopes of iodine. The Applicants therefore submit that since Carroll et al. do not claim a monofluoroalkyl group including ^{n}F where n=18 or 19 at the R position, and that the present invention does not claim a $CH_2CH=CH_2$ group or a $(CH_2)_nC_6H_5$ group where n=1-4 at the R position as recited in Carroll et al., Carroll et al. cannot anticipate the presently claimed invention. Therefore, the Applicants respectfully submit that the rejection under 102(e) is overcome.

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Further, the disclosure of Carroll et al. does not make Applicant's invention obvious. As mentioned above, the present invention claims a monofluoroalkyl group including ^{n}F where n=18 or 19 at the R position. By contrast, Carroll et al. teaches that the R position may be occupied by CH_3, $CH_2CH{=}CH_2$, or $(CH_2)_nC_6H_5$ where n=1-4 and does not teach or suggest that a monofluoroalkyl group at the R position is desirable to use or even possible to synthesize. Moreover, the Applicants submit that the Carroll et al. reference does not provide any motivation for one skilled in the art to attempt to incorporate a monofluoroalkyl group at the R position. One skilled in the art of neuropharmacology or synthetic bioorganic chemistry would not be able to predict, a priori, the utility or effectiveness of a monofluoroalkyl group bonded to the bridge nitrogen of a cocaine analog when it is used as a SPECT or PET imaging agent. Clearly, the language of the claims of the present invention are patentably distinguishable from the art of Carroll et al., and therefore the Applicants submit that the present invention is not obvious over the work of Carroll et al.

The Examiner has rejected claims 29-36 under 35 USC §103 as being unpatentable over Carroll et al., and in view of Nosco et al., and Wilbur et al. The Applicants respectfully traverse this rejection.

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The Applicants have amended claims 29 and 33 to recite a kit for preparing an iodinated neuroprobe for mapping monoamine reuptake sites, the kit comprising a precursor of the formulas shown above wherein

R = a monofluoroalkyl group or H;

R′ = a C_nH_{2n+1} group where n=0-6;

X = I or $Sn(R"_1R"_2R"_3)$;

$R"_1$ = a C_nH_{2n+1} group where n=1-6, or an aryl group;

$R"_2$ = a C_nH_{2n+1} group where n=1-6, or an aryl group;

$R"_3$ = a C_nH_{2n+1} group where n=1-6, or an aryl group;

Y = H; and

an oxidizing agent, wherein the precursor and the oxidizing agent are to be reacted in the presence of a radioisotope source.

The Applicants submit that the H substituent at the R position is supported in the specification on page 13, lines 13 and 18, and in Example 4, page 20, and therefore no new material has been added to the claims by the addition of H at the R position.

Applicants have further amended claims 32 and 36 to recite that the radioisotope source is a reagent of the formula $^{18}FC_nH_{2n}L$ where n=0-6 and L is a leaving group. The amendments to claims 32 and 36 more clearly define the scope of the invention and alleviate confusion with the "X" substituent of independent claims 29 and 33.

Nosco discloses a method of preparing radiopharmaceutical

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compositions comprising complexes of technetium-99m, and a kit for preparing such compositions. In particular, Nosco discloses reacting radioactive technetium-99m in the form of a pertechnetate in the presence of a reducing agent and an optional chelator and a complexation ligand (col. 5, lines 26-30, col. 6, lines 3-28, col. 6, lines 44-45).

The Applicants submit that the patent of Nosco does not teach or suggest a kit that employs an oxidizing agent "wherein the precursor and the oxidizing agent are to be reacted in the presence of a radioisotope source." Moreover, the broad language of Nosco stating that

> In connection with the comparatively short half-life of radionuclides it is often nearly impossible to deliver the ready-to-use labelled product to the user. In such cases it is desirable to place the various reaction components at the user's disposal in a so-called kit. By means of the kit, the user himself can carry out the labelling reaction with the radionuclide in the clinical hospital or laboratory at any desired moment.

does not teach, suggest, or even hint of reacting a precursor of a neuroprobe with an oxidizing agent in the presence of a radioisotope source. The Applicants argue that Nosco cannot claim all chemical kits, and that one of ordinary skill in the art of radiochemical kits could not develop the kit of the present invention given the broad language of Nosco cited by the Examiner. Therefore, the Applicants assert that Nosco, either alone or in combination with any other of the references of record, does not

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teach or suggest Applicants' invention, and that this rejection is overcome.

Wilbur et al. disclose vinyl-substituted radiohalogen conjugates useful for protein labeling, and kits for clinical use. In particular, Wilbur et al. disclose that vials or sets of vials containing certain precursors can be provided in combination with "the appropriate buffers and other reagents such that introduction of a radiohalogen will give the desired radiohalogentated molecule" (col. 13, lines 28-38). Further, Wilbur et al. disclose the use of oxidizing agents to produce derivatized glycoproteins that provide attachment sites for radiohalogenated molecules (col. 7, lines 55-62).

The present invention, by contrast, claims a kit for preparing an iodinated neuroprobe for mapping monoamine reuptake sites comprising a precursor of the formulae shown above wherein

R = a monofluoroalkyl group or H;

R' = a C_nH_{2n+1} group where n=0-6;

X = I or $Sn(R"_1R"_2R"_3)$;

$R"_1$ = a C_nH_{2n+1} group where n=1-6, or an aryl group;

$R"_2$ = a C_nH_{2n+1} group where n=1-6, or an aryl group;

$R"_3$ = a C_nH_{2n+1} group where n=1-6, or an aryl group; and

Y = H; and

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an oxidizing agent, wherein the precursor and the oxidizing agent are to be reacted in the presence of a radioisotope source.

The Applicants respectfully submit that Wilbur et al. do not teach or suggest that a kit is useful for preparation of a radioiodinated neuroprobe as claimed in the present invention. Moreover, the Applicants submit that the statement by Wilbur et al. that "the appropriate buffers and other reagents such that introduction of a radiohalogen will give the desired radiohalogentated molecule" (col. 13, lines 28-38) is insufficient to make the present invention obvious, and does not teach or suggest that a radioactive isotope of iodine may be incorporated into a cocaine analog. One skilled in the art of organic chemistry would immediately recognize that radiohalogens may be introduced into substrate molecules by a variety of methods, e.g., nucleophilic or electrophilic displacement, free radical reactions, etc., and that this broad statement does not teach or suggest to the skilled artisan that the desired product may be produced with an oxidizing agent.

The Applicants further submit that the present invention and the work of Wilbur et al. use oxidizing agents for completely different purposes, and that the oxidizing chemistry disclosed by Wilbur et al. will not occur, and, in fact, does not occur in the present invention. As recited in claims 29 and 33, the kit of the present invention employs an oxidizing agent to facilitate

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attachment of a radiohalogen isotope (e.g., ^{131}I) to a neuroprobe precursor and does not disclose or suggest that an oxidizing agent will produce reactive functional groups as disclosed by Wilbur. By contrast, Wilbur et al. teach that the sugar moieties of glycoproteins may be derivatized with an oxidizing agent to prepare reactive aldehyde groups that will provide reaction sites for a radiohalogenated molecule (col. 7, lines 55-62). Therefore, Wilbur et al. discloses use of an oxidizing agent to attach a previously radiohalogenated molecule to a glycoprotein. Wilbur et al. does not teach, suggest, or even hint of using an oxidizing agent as a catalyst for the attachment of a radiohalogen isotope to a substrate neuroprobe or any other small biomolecule. Therefore, based on the reasons recited above, the Applicants assert that one skilled in the art of neuropharmacology and organic chemistry would not look to the work of Wilbur et al. when faced with the problem of developing a kit that allows for the addition of a radiohalogen to a neuroprobe derivative using an oxidative catalyst. The Applicants submit that the language of the claims of the present invention are patentably distinguishable from the art of Wilbur et al., and therefore the disclosure of Wilbur et al. does not make the kit of the present invention obvious. Therefore, the Applicants submit that this rejection is overcome.

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The Applicants submit that all claims are in condition for allowance and respectfully request reconsideration and early favorable action by the Examiner.

If the Examiner believes a telephone conference would aid in the continued prosecution of this application, the Examiner is invited and encouraged to contact the Applicants' representative at the telephone number listed below.

Respectfully submitted,

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